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Wnt pathway activation functionally reprograms human antigen-specific T cells

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Polyfunctionality is a hallmark of protective immunity, yet the molecular mechanisms governing polyfunctional T cells are poorly understood. After TCR activation, naïve $CD8^+$ T cells undergo proliferation and differentiation, which lead to effector functions and memory subset development. However only a portion of activated T cells develop into memory $CD8^+$ T cells and with chronic stimulation become terminally differentiated and exhausted $CD8^+$ T cells, as defined by $CCR7^-/CD45RA^+$, and functionally impair effective immune responses [1]. We therefore probed the ability to reverse terminally differentiated antigen-specific cells using pharmacological agents. Stimulating human memory $CD8^+$ T cells with cognate TCR stimulation in the presence of Wnt agonist enhances polyfunctionality and stemness. Both M1-influenza$^+$ and CMV^+ $CD8^+$ T cell responses were reprogrammed and revealed sustained effects from initial Wnt pathway activation *in vitro*. Future work with cancer antigens and reprogramming of differentiated $CD8^+$ responses could lead to improved *in vitro* culture conditions for adoptive immunotherapy.

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